March 22 2019

PUBLIC COMMENT PERIOD FOR: - "Draft Hot Spots Cancer Inhalation Unit Risk Factors for Cobalt and Cobalt Compounds."
PRELIMINARY COMMENTS ON: - "Technical Support Document for Cancer Potency Factors; Appendix B; Public Comment Draft; March 2019."

TO THE OFFICE OF ENVIRONMENTAL HEALTH ASSESSMENT (California)
The Cobalt Institute (CI) is a global, non-profit trade association composed of producers, users, recyclers, and traders of cobalt (Co). We promote the sustainable and responsible production and use of cobalt in all its forms. The CI acts as a knowledge center for governments, agencies, industry, the media and the public on all matters concerning Co and Co containing substances. Our technical expertise includes Co related health, safety, and environmental issues.

We welcome the opportunity to comment on your above document deriving cancer slope factors for Co and Co compounds. Based on a thorough scientific review, we would like to submit the following preliminary comments. These will be followed up and complemented with a more detailed response into the public consultation before April 22, 2019. The CI is aware of two workshops with the public, planned to take place in California on March 26 and 28. Given the timing of these, CI wishes to provide this preliminary submission before those two workshops take place.

In summary, we are concerned that the combination of several single very precautionary assumptions and approaches results in a "multiplication of conservatism" that in turn results in a significant overestimation of risk.

We thank you for your attention to these comments, and we look forward to providing details and references to further corroborate our concerns. At this time, the CI considers it is important to emphasize the following points:

1 – In vivo genotoxicity of Co metal and Co compounds (referred to as "Co compounds" from here on)
The assumption of in vivo genotoxicity of Co compounds is based on data from studies with a low "Klimisch score", mainly based on non-relevant route of exposure (intra-peritoneal injection), low reliability based on flaws in reporting, and the fact that these studies did not follow OECD guidelines for genotoxicity testing. We would like to highlight to OEHHA an OECD review of 2014 (https://hpvchemicals.oecd.org/ui/handler.axd?id=e5e60085-1f3f-4df5-92f6-8f32c26c3082) which concludes lack of in vivo genotoxicity of Co compounds, following a stringent quality-, reliability- and relevance screening of the genotoxicity database of Co compounds. This conclusion is also reflected in recent publications (Kirkland et al, 2015 and Lison et al, 2018).

2 - Assumption of "independence" of tumors in Co inhalation studies
The proposed mode of action (MoA) of Co related inhalation carcinogenicity is induction of hypoxia and inflammation in the lung (see e.g. Lison et al, 2018). Some of the systemic tumors observed in the NTP inhalation studies are well-established responses that are secondary to hypoxia and respiratory distress (adrenal pheochromocytoma in rats (Ozaki et al., 2002)). The assumption of independence of the tumors observed in the Co NTP inhalation studies is not supported by the MoA of Co related inhalation carcinogenicity, and may lead to a severe overestimation of the potency of Co.

3 – Assumption of low solubility of Co metal powder
While Co metal powder is poorly soluble in water, it is in fact moderately to highly soluble in biological fluids, such as interstitial, alveolar or lysosomal artificial lung fluids. Data on the bioelution of several Co

18 Jeffries Passage, Guildford, GU1 4AP, UK
Tel: +44 1483 578877 email: info@cobaltinstitute.org Fax: +44 1483 567042
www.cobaltinstitute.org

compounds in lung fluid has led to the grouping of Co metal powder with the "soluble salts" (Co sulfate, Co chloride, Co nitrate and Co acetate) in one group of Co compounds classified as inhalation carcinogens (Carc 1B). This group of compounds is characterized by the induction of an inflammatory response and hypoxia in the lung following inhalation exposure. The similarity in effects caused by this group of substances has led to the conclusion that the toxicity of Co compounds is related to the Co ion, and that the magnitude of effect is related to the Co ion dose-to-target. This also inherently assumes that dose-to-target is critical for the magnitude of effect, and not differences in the potency between Co substances. This assumption is confirmed by the evaluation of the dose-response of Co exposure (from Co sulfate and Co metal powder) across all exposure concentrations in both NTP studies. The combination of both Co compounds into one dose response curve results in very good model fit, and the indication that the model can predict exposure-responses at relevant (low) exposures. A detailed report on benchmark dose (BMD) modeling of the complete animal dataset (Co metal powder and Co sulfate) will be provided with the detailed response to be submitted before April 22, 2019.
It is important to note that there are substances with negligible solubility in biological fluids (e.g., Co_3O_4 and CoS). Bioelution data will be provided in the detailed response, indicating that these "biologically insoluble" substances should not be grouped with Co metal powder for the inhalation toxicity endpoint.

4 - Calculation of BMDL5 with Co metal data only

A serious concern arises relating to the use of the BMD model in the context of the Co metal data alone. At the lowest dose, 30% of the female rats and 50% of the male rats had lung tumors. It is generally recommended to use the BMD model within a dose-response data set (as an interpolation). Extrapolation from high dose/high response data into areas of lower responses (e.g. BMD10 or 05) that are far outside the data results in high uncertainty and very large differences between BMDU and BMDL (BMD upper and lower confidence limits). The ratio between BMDU and BMDL is used as an indicator of the ability of the model to make a prediction at the effect level that is modeled, e.g. 5%. A ratio between 1 and 10 is seen as indication that the model is able to make a prediction (the closer to 1 the better the prediction). Preliminary investigation of the BMDL05 based on Co metal data alone shows that the ratio between BMDU and BMDL at 5% risk is close to 40, demonstrating the high uncertainty of the modeled BMD05 values. This uncertainty is significantly reduced when the Co sulfate data are included in the dose response modeling, as all Co sulfate exposures were lower than those applied in the Co metal study when compared on the Co equivalent basis.
The points related to the use and interpretation of BMD data will be provided in detail into the public consultation as a follow-up to this preliminary response.

In closing, the CI trusts our comments provided above are helpful to provide a better understanding of the reasons for our concerns. We would be pleased to discuss any questions you may have.

Yours,

Simon G Cook, Ph D
Vice President – Global Regulation
SCook@cobaltinstitute.org

Ruth Danziesen, Ph D, DABT
Toxicologist
RDanzeisen@cobaltinstitute.org